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(57) Abstract

A buccal aerosol spray or capsule using a polar solvent has now been developed which provides biologically active compounds for rapid absorption through the oral mucosa, resulting in fast onset of effect. The buccal aerosol spray of the invention comprises: polar solvent 5-50 %, active compound 0.0025-40 %, flavoring agent 0.05-5%. The soft bite gelatin capsule of the invention comprises as fill composition: polar solvent 75-99 %, emulsifier 0-20 %, active compound 0.0003-35 %, and flavoring agent 0.05-60 %.

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TITLE OF THE INVENTION

BUCCAL POLAR SPRAY OR CAPSULE

BACKGROUND OF THE INVENTION

It is known that certain biologically active compounds are better absorbed through the oral mucosa than through other routes of administration, such as through the stomach or intestine. However, formulations suitable for such administration by these latter routes present their own problems. For example, the biologically active compound must be compatible with the other components of the composition such as propellants, solvents, etc. Many such formulations have been proposed. For example, U.S.P. 4,689,233, Dvorsky et al., describes a soft gelatin capsule for the administration of the anti-coronary drug nifedipine dissolved in a mixture of polyether alcohols. U.S.P. 4,755,389, Jones et al., describes a hard gelatin chewable capsule containing nifedipine. A chewable gelatin capsule containing a solution or dispersion of a drug is described in U.S.P. 4,935,243, Borkan et al. U.S.P. 4,919,919, Aouda et al, and U.S.P. 5,370,862, Klokkers-Bethke, describe a nitroglycerin spray for administration to the oral mucosa comprising nitroglycerin, ethanol, and other components. An orally administered pump spray is described by Cholcha in U.S.P. 5,186,925. Aerosol compositions containing a hydrocarbon propellant and a drug for administration to a mucosal surface are described in U.K. 2,082,457, Su, U.S.P. 3,155,574, Silson et al., U.S.P. 5,011,678, Wang et al., and by Parnell in U.S.P. 5,128,132. It should be noted that these references discuss bioavailability of solutions by inhalation rather than through the membranes to which they are administered.

SUMMARY OF THE INVENTION

A buccal aerosol spray or soft bite gelatin capsule using a polar solvent has now been developed which provides biologically active compounds for rapid absorption through the oral mucosa, resulting in fast onset

of effect.

The buccal aerosol spray compositions of the present invention, for transmucosal administration of a pharmacologically active compound soluble in a pharmacologically acceptable polar solvent comprising in weight% of total composition: polar solvent 75-99.8%, active compound 0.0025-40%, suitably additionally comprising, by weight of total composition a flavoring agent 0.05-5%. Preferably the composition comprises: polar solvent 75-99%, active compound 0.025-20%, flavoring agent 0.1-2.5%; most suitably polar solvent 75-98%, active compound 0.125-12.5%, flavoring agent 0.1-2.5%.

The soft bite gelatin capsules of the present invention for transmucosal administration of a pharmacologically active compound, at least partially soluble in a pharmacologically acceptable polar solvent, having charged thereto a composition comprising in weight % of total composition: polar solvent 40-99.8%, emulsifier 0-20%, active compound 0.0003-35%, provided that said composition contains less than 10% of water, suitably additionally comprising, by weight of the composition: flavoring agent 0.05-60%. Preferably, the soft bite gelatin capsule comprises: polar solvent 50-99.8%, emulsifier 0-15%, active compound 0.0003-26%, flavoring agent 0.5-55%; most suitably: polar solvent 70-99.5%, emulsifier 0-10%, active compound 0.015-24.0%, flavoring agent 0.1-50%.

It is an object of the invention to coat the mucosal membranes either with extremely fine droplets of spray containing the active compounds or a solution or paste therof from bite capsules.

It is also an object of the invention to administer to a mammalian need of same preferably man, a predetermined amount of a biologically active compound by this method or from a soft gelatin bite capsule.

A further object is a pump spray container containing a composition of the spray formulation, and a metered valve suitable for releasing from said container a predetermined amount of said composition.

The solvent is a low molecular weight, pharmacologically acceptable alcohol, water, glycerine or polyethylene glycol or mixtures thereof.

A further object is a soft gelatin bite capsule containing a composition as set forth above. The formulation may be in the form of a viscous solution or paste containing the active compounds. Although solutions are preferred, paste fills may also be used where the active compound is not soluble or only partially soluble in the solvent of choice. Where water is used to form part of the solvent or paste composition, it should not exceed 10% thereof. (All percentages herein are by weight unless otherwise indicated.)

The polar solvent is chosen such that it is compatible with the gelatin shell and the active compound. The solvent preferably dissolves the active compound. However, other components wherein the active compound is not soluble or only slightly soluble may be used and will form a paste fill.

Soft gelatin capsules are well known in the art. See, for example, U.S.P. 4,935,243, Borkan et al., which is incorporated herein by reference for its teaching of such capsules. The capsules of the present invention are intended to be bitten into to release the low viscosity solution or paste therein, which will then coat the buccal mucosa with the active compounds. Typical capsules, which are swallowed whole or bitten and then swallowed, deliver the active compounds the stomach, which results in significant lag time before maximum blood levels can be achieved or subject the compound to a large first pass effect. Because of the enhanced absorption of the compounds through the oral mucosa and no chance of a first pass effect,

use of the bite capsules of the invention will eliminate much of the lag time, resulting in hastened onset of biological effect. The shell of a soft gelatin capsule of the invention may comprise, for example: gelatine 50-75%, glycerine 20-30%, colorants 0.5-1.5%, water 5-10%, and sorbitol 2-10%.

The spray compositions of the invention are intended to be administered from a pump spray.

BRIEF DESCRIPTION OF THE DRAWING

The figure is a schematic diagram showing routes of absorption and processing of pharmacologically active substances in a mammalian system.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

The preferred active compounds of the present invention are nicotine, clemastine, testosterone, estradiol, progesterone, fluoxetine, and piroxicam in their nonionized form or as the free base of the pharmaceutically acceptable salts thereof (provided, for the aerosol or spray compositions, they are soluble in the spray solvent). These compounds are soluble in the non- polar solvents of the invention at useful concentrations or can be prepared as pastes at useful concentrations. These concentrations may be less than the standard accepted dose for these compounds since there is enhanced absorption of the compounds through the oral mucosa. This aspect of the invention is especially important when there is a large (40-99.99%) First pass effect.

As solvents for the sprays there may be used low molecular weight polyethyleneglycols (PEG) of 400-1000 Mw (preferably 400-600). Low molecular weight alcohols and polyols, such as glycerin may also be present and water may also be used.

Suitable solvents for the capsules include low molecular weight polyethyleneglycols (PEG) of 400-1000 Mw (preferably 400-600). Low

molecular weight alcohols and polyols, such as glycerin may also be present and water may also be used. However, these should only be used sparingly in the bite capsule compo-sitions as they may migrate into the gelatin shell and weaken it.

It is expected that some glycerin and water used to make the gelatin shell will migrate from the shell to the fill during the curing of the shell. Likewise, there may be some migration of components from the fill to the shell during curing and even throughout the shelf-life of the capsule. Therefore, the values given herein are for the compositions as prepared, it being within the scope of the invention that minor variations will occur.

The preferred flavoring agents are synthetic or natural oil of peppermint, oil of spearmint, citrus oil, fruit flavors, chocolate, sweeteners (sugars, aspartame, saccharin, etc.), and combinations thereof.

The active substances include the active compounds selected from the group consisting of alkaloids, anti histamines, steroid hormones, non-steroidal anti-inflammatories, analgesics and anti-depressants, benzo-diazepines, such as tamezepam.

Clemastine hydrogen fumarate is a known (Tavist®, Sandoz) anti-histamine. Both the spray and capsule of the invention advantageously coat the oral mucosa with an immediately available dose of clemastine which can be rapidly absorbed. This is highly desirable, as during an acute asthma attack.

Nicotine is a component of tobacco products which is considered addictive. Smokers wishing to stop smoking have a dual problem. First, is the addictive properties of nicotine itself. Second, is that the habit is associated with smoking activities, i.e., puffing, inhaling, etc. Both the spray and capsule of the invention dissociate these two problems. By

presenting nicotine in a form which can be readily absorbed, the spray and capsule allow the smoker to temporarily continue nicotine use but terminate smoking. Once the habit of smoking is stopped, the former smoker can then be weaned off nicotine use, as by less frequent use and/or by use of a lower concentration spray or capsule. Advantageously, during this regimen, the user is exposed to none of the carcinogens present in tobacco smoke.

Testosterone is a hormone produced by gonadal cells. Testosterone, especially the esters thereof (e.g., acetate, propionate, enanthate, and cypionate), is used in the treatment of hypogonadism.

Estradiol is an estrogen steroid secreted from the ovaries. Estradiol, especially the esters thereof (e.g., diacetate, and benzoate), is used as estrogen replacement therapy, especially in post-menopausal women.

Progesterone is a hormone produced by the corpus luteum. Fluoxetine is an antidepressant also known as Prozac. Piroxicam is a known (Feldene®, Pfizer) anti-inflammatory.

The formulations of the present invention comprise an active compound or a pharmaceutically acceptable salt thereof. The term "pharmaceutically acceptable salts" refers to salts prepared from pharmaceutically acceptable non-toxic acids or bases including organic and inorganic acids or bases.

When an active compound of the present invention is acidic, salts may be prepared from pharmaceutically acceptable non-toxic bases. Salts derived from all stable forms of inorganic bases include aluminum, ammonium, calcium, copper, iron, lithium, magnesium, manganese, potassium, sodium, zinc, etc. Particularly preferred are the ammonium,

calcium, magnesium, potassium, and sodium salts. Salts derived from pharmaceutically acceptable organic non-toxic bases include salts of primary, secondary, and tertiary amines, substituted amines including naturally occurring substituted amines, cyclic amines and basic ion-exchange resins such as arginine, betaine, caffeine, choline, N,N'-dibenzylethylenediamine, diethylamine, 2-diethylaminoethanol, 2-dimethylaminoethanol, ethanolamine, ethylenediamine, N-ethylmorpholine, N-ethylpiperidine, glucamine, glucosamine, histidine, isopropylamine, lysine, methylglucosamine, morpholine, piperazine, piperidine, polyamine resins, procaine, purine, theobromine, triethylamine, trimethylamine, tripropylamine, etc.

When an active compound of the present invention is basic, salts may be prepared from pharmaceutically acceptable non-toxic acids. Such acids include acetic, benzenesulfonic, benzoic, camphorsulfonic, citric, ethanesulfonic, fumaric, gluconic, glutamic, hydrobromic, hydrochloric, isethionic, lactic, maleic, mandelic, methanesulfonic, mucic, nitric, pamoic, pantothenic, phosphoric, succinic, sulfuric, tartaric, p-toluenesulfonic, etc. Particularly preferred are citric, hydrobromic, maleic, phosphoric, sulfuric, and tartaric acids.

In the discussion of methods of treatment herein, reference to the active compounds is meant to also include the pharmaceutically acceptable salts thereof. While certain formulations are set forth herein, the actual amounts to be administered to the mammal or man in need of same are to be determined by the treating physician.

The invention is further defined by reference to the following examples, which are intended to be illustrative and not limiting.

EXAMPLE 1

Clemastine Spray

A spray of the invention comprises the following formulation:

	Amount	Preferred Amount	Most-Preferred Amount
Polar solvent	75-99%	90-99%	97-99%
Clemastine fumarate	0.12-12.5%	0.25-7.25%	0.25-6.5%
Flavoring agent	0.05-5%	0.1-2.5%	0.2-2%

It is particularly preferred to formulate the spray delivering 1.34mg/activation:

	Amount
Polar solvent:	
Ethanol	66%
Water	31%
Clemastine fumarate	2.8%
Peppermint Oil	0.2%

EXAMPLE 2

Nicotine Spray

A spray of the invention comprises the following formulation:

	Amount	Preferred Amount	Most-Preferred Amount
Polar solvent	75-99.8%	96-99.8%	96-99.8%
Nicotine	0.0125-10%	0.125-2.5%	0.2-1.15%
Flavoring agent	0.05-5%	0.1-2.5%	0.2-2.0%

It is particularly preferred to formulate the spray delivering 0.5mg/activation:

	Amount
Polar solvent:	
Ethanol	49.37%
Water	49.37%
Nicotine	1.06%
Peppermint Oil	0.2%

EXAMPLE 3

Nicotine Sulfate

A spray of the invention comprises the following formulation:

	Amount	Preferred Amount	Most-Preferred Amount
Polar solvent	75-99.8%	96-99.8%	96-99.8%
Nicotine Sulfate	0.0125-10%	0.125-2.5%	0.2-2.0%
Flavoring agent	0.05-5%	0.1-2.5%	1-2%

It is particularly preferred to formulate the spray for 0.5mg of nicotine sulfate:

	Amount
Polar solvent:	
Ethanol	9.84%
Water	88.9%
Nicotine Sulfate	1.06%
Peppermint Oil	0.2%

EXAMPLE 4

Fluoxetine Hydrochloride Spray

A spray of the invention comprises the following formulation:

	Amount	Preferred Amount	Most-Preferred Amount
Polar solvent	75-99%	75-98%	75-95%
Fluoxetine Hydrochloride	0.125-25%	2.5-20%	5-12.5%
Flavoring agent	0.05-5%	0.1-2.5%	0.1-2.0%

It is particularly preferred to formulate the spray delivering 5mg/activation:

	Amount
Polar solvent:	
Ethanol	48.4%
Water	10.0%
Polyethyleneglycol	30.0%
Fluoxetine HCl	10.6%
Oil of Orange	1.0%

EXAMPLE 5

Testosterone Spray Delivering 3mg/Activation

A spray of the invention comprises the following formulation:

	Amount	Preferred Amount	Most-Preferred Amount
Polar Solvent	55-99%	75-95%	85-93%
Testosterone	0.12-10%	0.25-7.5%	0.25-6.5%
Flavoring Agent	0.05-3%	0.1-2.5%	0.1-2.5%

It is particularly preferred to formulate the spray:

	Amount
Polar Solvent:	
Water	10%
Polyethyleneglycol	65%
Ethanol	16.6%
Testosterone	6.4%
Orange Aroma	1.0%
Oil of Citrus	1.0%

EXAMPLE 6

Estradiol Spray Delivering 0.1mg/Activation

A spray of the invention comprises the following formulation:

	Amount	Preferred Amount	Most-Preferred Amount
Polar Solvent	75-99%	75-95%	85-99%
Estradiol	0.0025-2.5%	0.025-1.5%	0.125-1.0%
Flavoring Agent	0.05-3%	0.1-2.5%	1-2%

It is particularly preferred to formulate the spray:

	Amount
Polar Solvent:	
Water	10%
Polyethyleneglycol	75%
Ethanol	13.79%
Estradiol	0.21%
Peppermint	1.0%

EXAMPLE 7

Progesterone Spray Delivering 0.32mg/Activation

A spray of the invention comprises the following formulation:

	Amount	Preferred Amount	Most-Preferred Amount
Propellent	55-99%	75-99.8%	85-99.5%
Progesterone	0.12-10%	0.25-6.25%	0.25-1%
Flavoring Agent	0.05-3%	0.1-2.5%	1-2%

It is particularly preferred to formulate the spray:

	Amount
Polar Solvent:	
Water	10%
Polyethyleneglycol	75%
Ethanol	13.32%
Progesterone	0.68%
Peppermint	1.0%

EXAMPLE 8

Clemastine Bite Capsule

A bite capsule of the invention comprises the following fill formulation:

	Amount	Preferred Amount	Most-Preferred Amount
Polar solvent	55-99%	66-97%	85-99.5%
Emulsifier	0-20%	0-15%	0-10%
Clemastine fumarate	0.1-4%	0.03-3%	0.04-1.5%
Flavoring agent	0.05-5%	0.1-2.5%	0.1-2.5%

It is particularly preferred to formulate the composition fill for a 1.34mg capsule:

	Amount
Polar Solvent:	
Polyethyleneglycol	89.6%%
Water	5.3%
Glycerine	4.4%
Clemastine fumarate	0.50%
Peppermint Oil	0.1%
Saccharine	0.1%

EXAMPLE 9

Testosterone Bite Capsule

A bite capsule of the invention comprises the following fill formulation:

	Amount	Preferred Amount	Most-Preferred Amount
Polar solvent	55-99%	66-97%	85-99.5%
Emulsifier/wetting agents	0-20%	0-15%	0-10%
Testosterone*	0.01-3.7%	0.4-3%	0.7-2%
Flavoring agent	0.05-5%	0.1-2.5%	0.1-2.5%

*or esters thereof, preferably, the acetate, propionate, and enenthate esters

It is particularly preferred to formulate the fill composition for the 5mg capsule:

	Amount
Polar solvent:	
Polyethyleneglycol	85.0%
Glycerine	6.15%
Lecithin	6.0%
Testosterone	1.85%
Peppermint Oil	1.0%

EXAMPLE 10

Estradiol Bite Capsule

A bite capsule of the invention comprises the following fill formulation:

	Amount	Preferred Amount	Most-Preferred Amount
Polar solvent	75-99%	75-99.8%	85-99.5%
Emulsifier/wetting agents	0-20%	0-15%	0-10%
Estradiol*	0.0003-2%	0.003-0.75%	0.02-0.2%
Flavoring agent	0.05-5%	0.1-2.5%	0.1-2.5%

*or esters thereof, preferably, the diacetate and benzoate esters

It is particularly preferred to formulate the fill composition for a 0.5mg capsule:

	Amount
Polar solvent:	
Polyethyleneglycol	85%
Glycerine	8.82%
Lecithin	5.0%
Estradiol	0.18%
Oil of Peppermint	1.0%

EXAMPLE 11

Progesterone Bite Capsule

A bite capsule of the invention comprises the following fill formulation:

	Amount	Preferred Amount	Most-Preferred Amount
Polar solvent	75-99.8%	75-98.8%	85-99.5%
Emulsifier/wetting agents	0-20%	0-15%	0-10%
Progesterone	0.0003-4%	0.0003-3%	0.75-2%
Flavoring agent	0.05-5%	0.1-2.5%	0.1-2.5%

It is particularly preferred to formulate the fill formulation for a 3mg capsule:

	Amount
Polar solvent:	
Polyethyleneglycol	85%
Glycerine	7.89%
Lecithin	5.0%
Progesterone	1.11%
Oil of Peppermint	1.0%

EXAMPLE 12

Fluoxetine Bite Capsule

A bite capsule of the invention comprises the following fill formulation:

	Amount	Preferred Amount	Most-Preferred Amount
Polar solvent	75-99.8%	75-99.8%	85-99.5%
Emulsifier/wetting agents	0-20%	0-15%	0-10%
Fluoxetine HCl	0.2-9.25%	0.4-6%	0.75-4%
Flavoring agent	0.05-5%	0.1-2.5%	0.5-3%

It is particularly preferred to formulate the fill formulation for a 5mg capsule:

	Amount
Polar solvent:	
Polyethyleneglycol	85%
Glycerine	7.15%
Lecithin	5.0%
Fluoxetine HCl	1.85%
Oil of Peppermint	1.0%

EXAMPLE 13

Piroxicam Bite Capsule

A bite capsule of the invention comprises the following fill formulation:

	Amount	Preferred Amount	Most-Preferred Amount
Polar solvent	75-99.8%	75-99.8%	95-99.5%
Emulsifier/wetting agents	0-20%	0-15%	0-10%
Piroxicam	0.02-9.25%	0.4-4%	0.75-4%
Flavoring agent	0.05-5%	0.1-4.5%	0.5-3%

It is particularly preferred to formulate the fill formulation for a 5mg capsule:

	Amount
Polar solvent:	
Polyethyleneglycol	85%
Glycerine	7.5%
Lecithin	5.0%
Piroxicam	1.85%
Oil of Peppermint	1.0%

EXAMPLE 14

Clemastine Fumarate with Phenylpropanolamine Hydrocyloride Bite Capsule

A bite capsule of the invention comprises the following fill formulation:

	Amount	Preferred Amount	Most-Preferred Amount
Polar solvent	40-99%	50-98%	70-98%
Emulsifier	0-20%	0-15%	0-10%
Clemastine fumarate	0.01-1.85%	0.03-0.74%	0.05-0.185%
Phenylpropanolamine HCl	1-30%	1.5-20%	1.8-10%
Flavoring agent	0.05-5%	0.1-2.5%	0.1-2.5%

It is particularly preferred to formulate the composition fill for a clamastine 1.34mg/25mg phenylpropanolamine capsule:

	Amount
Polar Solvent:	
Polyethyleneglycol	78.73%
Water	5.3%
Glycerine	4.4%
Clemastine fumarate	0.5%
Phenylpropanolamine HCl	9.2%
Saccharine	0.37%
Peppermint Oil	1.5%

EXAMPLE 15

Clemastine/Pseudoephedrine Bite Capsule

A bite capsule of the invention comprises the following fill formulation:

	Amount	Preferred Amount	Most-Preferred Amount
Polar solvent	40-99%	60-95%	70-90%
Emulsifier	0-20%	0-15%	0-10%
Clemastine fumarate	0.01-1.85%	0.03-0.74%	0.05-01.85%
Pseudoephedrine HCl	3-30%	5-25%	10-23%
Flavoring agent	0.05-5%	0.1-2.5%	0.1-2.5%

It is particularly preferred to formulate the composition fill for a 1.34mg clemastine fumerate/60mg pseudoephridrine HCl capsule:

	Amount
Polar Solvent:	
Polyethyleneglycol	65.71%%
Water	5.30%
Glycerine	4.40%
Clemastine fumarate	0.50%
Pseudoephedrine HCl	22.22%
Peppermint Oil	1.5%
Saccharine	0.37%

EXAMPLE 16

Nicotine 0.5mg Bite Capsule

A bite capsule of the invention comprises the following fill formulation:

	Amount	Preferred Amount	Most-Preferred Amount
Polar solvent	30-99.8%	35-99.8%	40-99.5%
Emulsifier/wetting agents	0-20%	0-15%	0-10%
Nicotine*	0.018-0.74%	0.037-0.37%	0.37-0.20%
Flavoring agent	0.05-60%	0.1-55%	0.5-50%

* or as nicotine sulfate

It is particularly preferred to formulate the fill for a 0.5mg capsule:

	Amount
Polar Solvent:	
Polyethyleneglycol	89.6%%
Water	5.5%
Glycerine	4.40%
Peppermint Oil	0.1%
Na Saccharine	0.1%
Nicotine	0.185%

WHAT IS CLAIMED IS:

1. A buccal aerosol spray composition for transmucosal administration of a pharmacologically active compound soluble in a pharmacologically acceptable polar solvent comprising in weight % of total composition: polar solvent 75-99.8%, active compound 0.0025-40%.

2. The composition of claim 1 additionally comprising, by weight of total composition: flavoring agent 0.05-5%.

3. The composition of claim 1 comprising: polar solvent 75-99%, active compound 0.025-20%, flavoring agent 0.1-2.5%.

4. The composition of claim 1 comprising: polar solvent 75-98%, active compound 0.125-12.5%, flavoring agent 0.1-2.5%.

5. The composition of Claim 1 wherein the solvent is a selected from the group consisting of C_{7-18} hydrocarbons of a linear or branched configuration, the alcohols thereof, the fatty acid esters of said alcohols.

6. The composition of Claim 1 wherein the solvent is miglyol.

7. The composition of Claim 1 wherein the active compound is selected from the group consisting of alkaloids, non-steroidal anti-inflammatories, analgesics, anti-histamines, steroid hormones, benzo-diazepams, and anti-depressants.

8. The composition of Claim 7 wherein the active compound is selected from the group consisting of nicotine, clemastine, testosterone, estradiol, progesterone, temazepam, fluoxetine, and piroxicam in their nonionized form or as the free base of the pharmaceutically acceptable salts

thereof.

9. The composition of Claim 2 wherein the flavoring agents are selected from the group consisting of synthetic or natural oil of peppermint, oil of spearmint, citrus oil, fruit flavors, sweeteners and combinations thereof.

10. The composition of Claim 2 of the formulation: polar solvent 75-99%, clemastine 0.12-10%, flavoring agent 0.05-5%.

11. The composition of Claim 2 of the formulation: polar solvent 75-99%, nicotine 0.0125-10%, flavoring agent 0.05-5%.

12. A method of administering a pharmacologically active compound to a mammal in needed of same, by spraying the oral mucosa of said mammal with a composition of claim 1.

13. The method of claim 12 wherein the amount of spray administered is predetermined.

14. A soft bite gelatin capsule for transmucosal administration of a pharmacologically active compound, at least partially soluble in a pharmacologically acceptable polar solvent, having charged thereto a fill composition comprising in weight % of total fill composition: polar solvent 50-99.8%, emulsifier 0-20%, active compound 0.0003-26%, provided that said composition contains less than 10% of water.

15. The capsule of claim 14 additionally comprising, by weight of the fill composition: flavoring agent 0.05-60%.

16. The soft bite gelatin capsule of Claim 14 comprising as the fill composition: polar solvent 50-99.8%, emulsifier 0-15%, active compound 0.0003-26%, flavoring agent 0.1-50%.

17. The soft bite gelatin capsule of Claim 14 comprising as the fill composition:polar solvent 70-99.5%, emulsifier 0-10%, active compound 0.015- 24.0%, flavoring agent 0.1-50%.

18. The capsule of Claim 14 wherein the solvent is selected from the group consisting of low molecular weight polyethyleneglycols (PEG) of 400-1000 MW, (C_2-C_{24}) fatty acid (C_2-C_6) esters, C_2-C_8 mono- and poly-alcohols, C_7-C_{18} hydrocarbons of a linear or branched configuration, the alcohols thereof, and the fatty acid esters of said alcohols.

19 The capsule of Claim 14 wherein the solvent is selected from low molecular weight polyethyleneglycols (PEG) of 400-600 MW, (C_2-C_{24}) fatty acid (C_2-C_6) esters and the triglycerides of said fatty acids.

20. The composition of Claim 14 wherein the active compound is selected from the group consisting of alkaloids, non-steroidal anti-inflammatories, analgesics, anti-histamines, steroid hormones, benzo-diazepams, and anti-depressants.

21. The capsule of Claim 14 wherein the active compound is nicotine, clemastine, testosterone, estradiol, progesterone, fluoxetine, or piroxicam in their nonionized form or as the free base of the pharmaceutically acceptable salts thereof.

22. The capsule of Claim 14 wherein the flavoring agents are synthetic or natural oil of peppermint, oil of spearmint, citrus oil, fruit flavors, or sweeteners and combinations thereof.

23. The capsule of Claim 14 comprising as the fill composition the formulation: polar solvent 75-99%, emulsifier 0-20%, clemastine fumarate 0.01-4%, flavoring agent 0.05-5%.

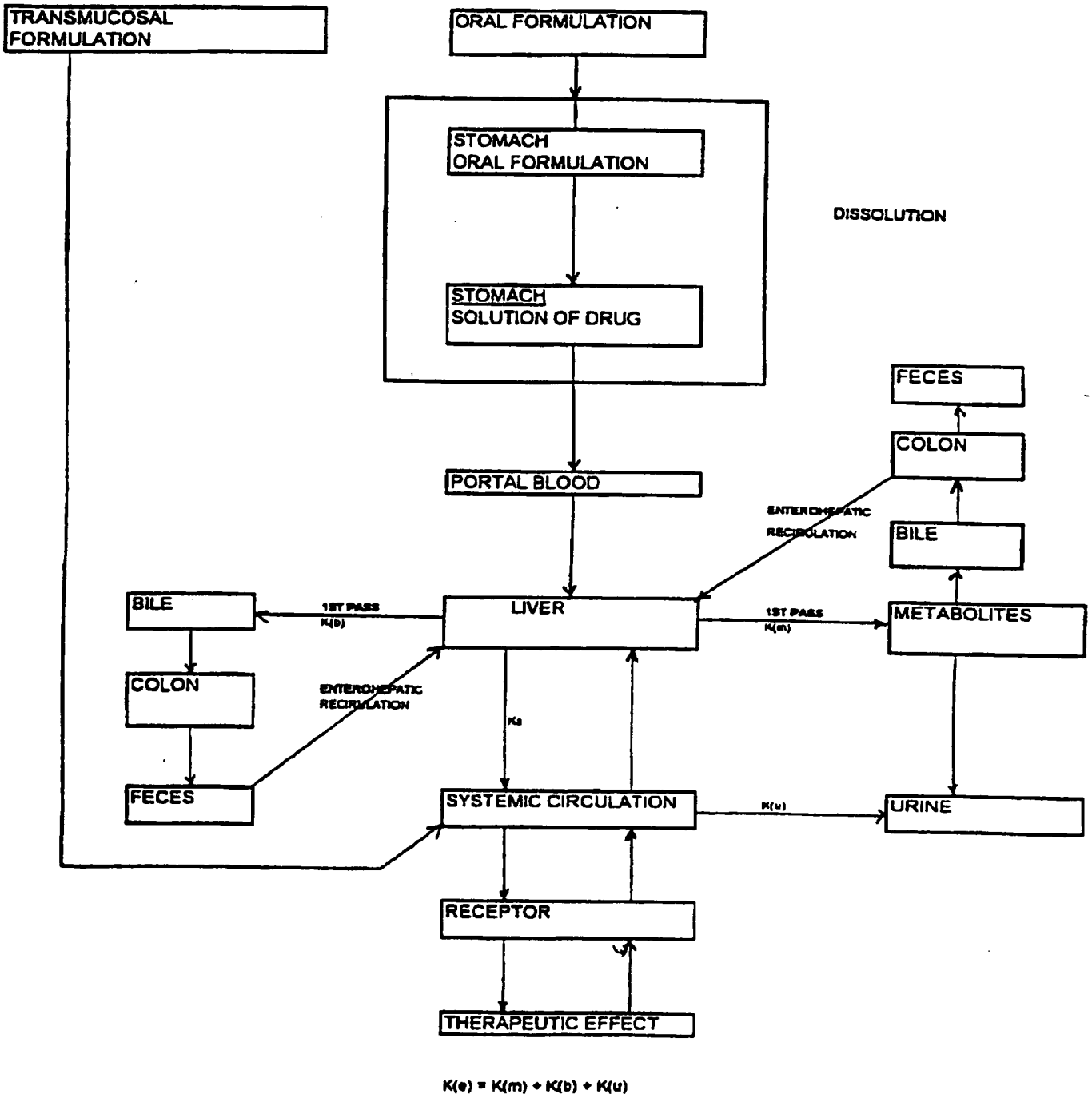
24. The capsule of Claim 14 comprising as the fill composition the formulation: polar solvent 55-99%, emulsifier 0-20%, a member selected from the group consisting of testosterone and the esters thereof 0.01-4%, flavoring agent 0.05-5%.

25. The capsule of Claim 14 comprising as the fill composition the formulation: polar solvent 65-99%, emulsifier 0-20%, estradiol 0.0003-2%, flavoring agent 0.05-5%.

26. The capsule of Claim 14 comprising as the fill composition the formulation: polar solvent 75-99.8%, emulsifier 0-20%, progesterone 0.0003-4%, flavoring agent 0.05-5%.

27. The capsule of Claim 14 comprising as the fill composition the formulation: polar solvent 75-99.8%, emulsifier 0-20%, fluoxetine HCl 0.02-9.5%, flavoring agent 0.05-5%.

28. The capsule of Claim 14 comprising as the fill composition the formulation: polar solvent 75-99.8%, emulsifier 0-20%, piroxicam 0.02-9.5%, flavoring agent 0.05-5%.


TRANSMUCOSAL FORMULATION
ORAL FORMULATION
STOMACH ORAL FORMULATION
DISSOLUTION
STOMACH SOLUTION OF DRUG
FECES
COLON
PORTAL BLOOD
ENTEROHEPATIC RECIRCULATION
BILE
BILE
1ST PASS K(b)
LIVER
1ST PASS K(m)
METABOLITES
COLON
ENTEROHEPATIC RECIRCULATION
Ks
FECES
SYSTEMIC CIRCULATION
K(u)
URINE
RECEPTOR
THERAPEUTIC EFFECT

$K(e) = K(m) + K(b) + K(u)$